ITW

Docket No.: 0020-5489PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Robert William WARD et al.

Application No.: 10/581,723 Confirmation No.: N/A

Filed: June 5, 2006 Art Unit: N/A

For: NOVEL COMPOUNDS Examiner: Not Yet Assigned

LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Subsequent to the filing of the above-identified application on June 5, 2006, attached hereto is the International Preliminary Report on Patentability issued by the International Bureau on behalf of the International Searching Authority. Please make this document of record for the above-identified application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or to credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Dated: JUL 18 2006

Respectfully submitted,

By G. Murphy Jr
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Attachments: **PCT/IPEA/416, PCT/IPEA/409**

PATENT COOPERATION TREATY

1001
4001

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

受付
18.6.13
津山特許事務所

PCT

To:

KAWAMIYA, Osamu et al.
Aoyama & Partners
IMP Building, 3-7, Shiromi
1-chome, Chuo-ku, Osaka-shi
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JAPON

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	09.06.2006
Applicant's or agent's file reference 664894	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/019455	17.12.2004	20.12.2003

Applicant
TANABE SEIYAKU CO., LTD. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Morancho Alcaine, N Tel. +49 89 2399-7462

Form PCT/IPEA/ 416 (January 2004)

外国方式

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 664894	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/JP2004/019455	International filing date *(day/month/year)* 17.12.2004	Priority date *(day/month/year)* 20.12.2003
International Patent Classification (IPC) or national classification and IPC INV. C07C233/87 A61K31/166 A61P7/00 A61P7/02 A61P9/00 A61P9/10 A61P11/00 A61P17/00 A61P19/00 A61P25/00 A61P25/28 A61P31/00 A61P31/22 A61P37/00 A61P37/08		
Applicant TANABE SEIYAKU CO., LTD. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 9 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand 21.01.2005	Date of completion of this report 09.06.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Albayrak, T Telephone No. +49 89 2399-7549

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/019455

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1, 2, 5, 6, 8-13, 15, 16, 18-22, 24, 25, 27-30	as originally filed
3, 4, 7, 14, 17, 23, 26	filed with telefax on 29.07.2005

Claims, Numbers

11-19	as originally filed
1-10	filed with telefax on 29.07.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/019455

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 13-15

because:

☒ the said international application, or the said claims Nos. 13-15 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	19
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-12,16-19
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

The subject-matter of claims 13-15 is related to subject-matter considered to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4) (a) (I) PCT).

For the assessment of the present claims 13-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The remaining claims 1-12 and 16-19 are regarded as industrially applicable.

Re Item V

Reference is made to the following document/s/:

D1: WO 99/36393 A (TANABE SEIYAKU CO., LTD; SIRCAR, ILA; GUDMUNDSSON, KRISTJAN, S; MARTIN) 22 July 1999 (1999-07-22)

D2: US 2003/027814 A1 (ISHIWATA HIROYUKI ET AL) 6 February 2003 (2003-02-06)

1. **Novelty**

Claim 19 lacks novelty over D2. The claimed compound is disclosed on page 8 of D2 (Art. 33(2) PCT).

The remaining claims are considered novel.

2. **Inventive step**

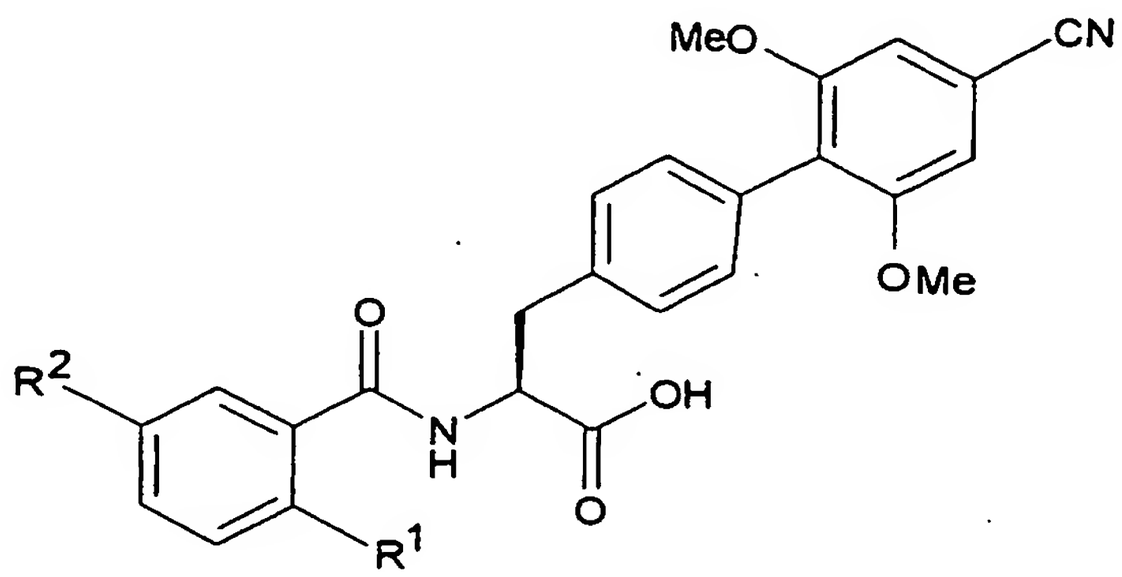
Although the compounds of claims 1-18 are not explicitly disclosed in the prior art they fall within the scope of the generic disclosure of D1.

Since D1 discloses the use of those compounds for the same therapeutic indication(s) claims 1-18 are regarded as a selection on the compounds of D1.

This could only be regarded as being inventive if a surprising/unexpected effect could be shown. However, this appears not to be the case.
For this reasons claims 1-18 are not regarded as being inventive (Art. 33(3) PCT).

DISCLOSURE OF INVENTION

The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

in which

R^1 is bromo; and

R^2 is halogen, C_{1-6}alkyl or C_{1-6}alkoxy.

Preferably R^2 is halogen or C_{1-6}alkoxy.

More preferably R^2 is fluoro, methoxy or ethoxy.

In a further aspect, the present invention provides E1-E7 (as described below) or a pharmaceutically acceptable derivative thereof, i.e.

(S)-2-{[1-(2-Bromo-5-ethoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid;

(*S*)-2-{[1-(2-Bromo-5-fluorophenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid;

(*S*)-2-{[1-(2-Bromo-5-methoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid;

(*S*)-2-{[1-(2-Bromo-5-methylphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid;

(*S*)-2-{[(2-Bromo-5-chlorophenyl)methanoyl]amino}-3-[4'-cyano-2',6'-dimethoxybiphenyl-4-yl]propionic acid;

(*S*)-2-{[(2,5-Dibromophenyl)methanoyl]amino}-3-[4'-cyano-2',6'-dimethoxybiphenyl-4-yl]propionic acid;

(*S*)-2-{[(5-(*iso*-Propoxy)-2-bromophenyl)methanoyl]amino}-3-[4'-cyano-2',6'-dimethoxybiphenyl-4-yl]propionic acid
or a pharmaceutically acceptable derivative thereof.

Throughout the present specification, unless otherwise stated:
the term "halogen" is used to describe a group selected from fluorine, chlorine, bromine or iodine;
the term " C_{1-6}alkyl" is used to describe a group or a part of the group comprising a linear or branched alkyl group containing from 1 to 6 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert butyl, pentyl or hexyl;
the term " C_{1-6}alkoxy" is used to describe a group or a part of the group wherein an oxygen atom is bound to the above mentioned C_{1-6}alkyl group; examples of such groups include methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, tert butoxy, pentoxy or hexoxy.

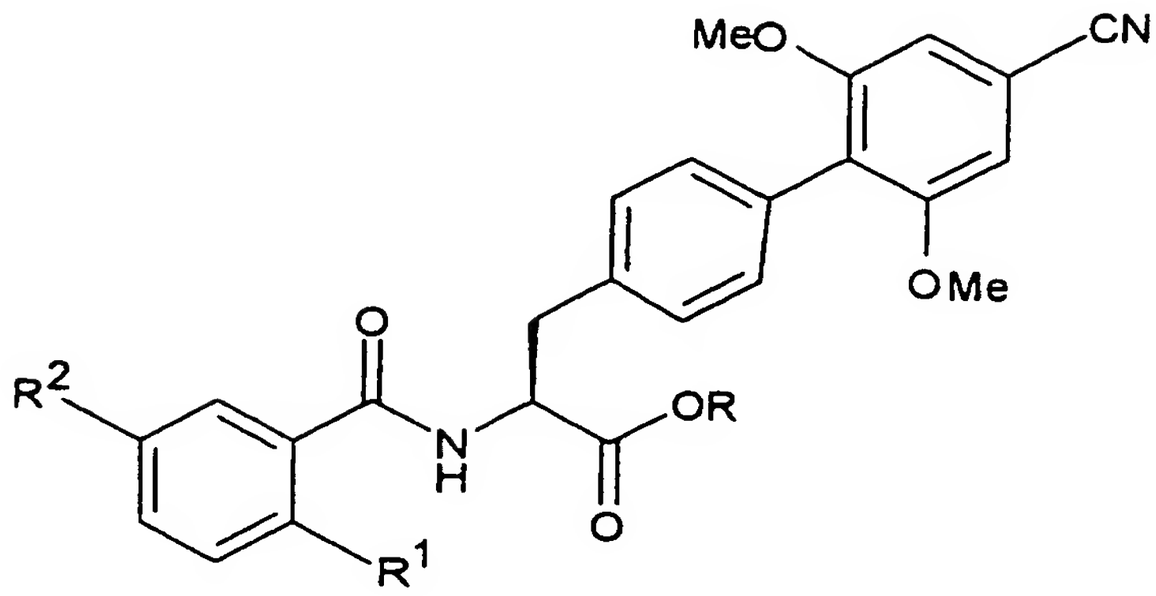
The characteristics of the present compounds are the introduction of a cyano group at the 4'-position of the biphenyl nucleus in combination with the claimed 2,5- di-substituted benzoyl group.

The compounds of the formula (I) or a pharmaceutically acceptable derivative thereof have potent inhibitory activity against α_4 integrin mediated cell adhesion. Further, it has been found that certain Examples show excellent bioavailability after oral administration and / or good systemic exposure.

E1, E2 and E3 (as described below) exhibit an advantageous combination of the above characteristics.

It will be appreciated that the compounds of formula (I) or a pharmaceutically acceptable derivative thereof may have more than one asymmetric carbon atoms and therefore may occur as diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or HPLC. A single stereoisomeric form of the compound may also be prepared from a corresponding optically pure intermediate or

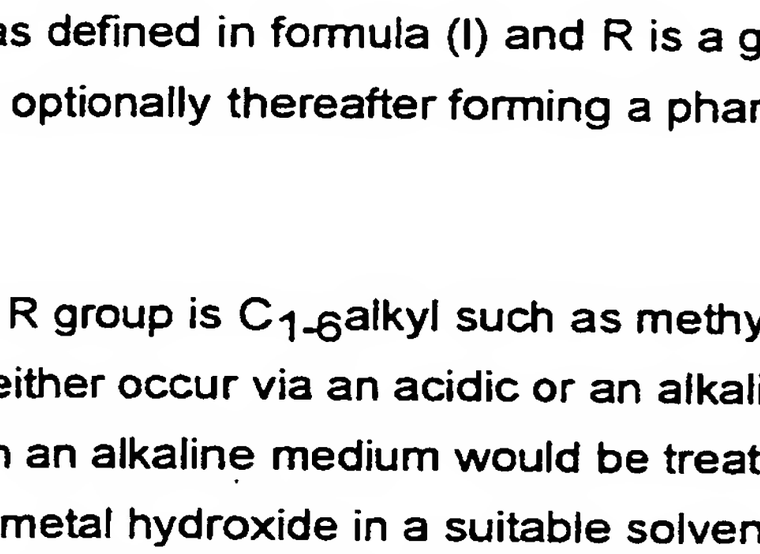


(II)

in which R^1 and R^2 are as defined in formula (I) and R is a group capable of forming a carboxylic acid ester and optionally thereafter forming a pharmaceutically acceptable derivative thereof.

An example of a suitable R group is C_{1-6}alkyl such as methyl or t-butyl, preferably methyl. Hydrolysis may either occur via an acidic or an alkaline medium. An illustration of hydrolysis in an alkaline medium would be treating the compound of formula (II) with an alkali metal hydroxide in a suitable solvent e.g. treatment with lithium hydroxide in aqueous tetrahydrofuran. An illustration of hydrolysis in an acidic medium would be treating the compound of formula (II) with a mineral acid in a suitable co-solvent at elevated temperature e.g. treatment with 5N hydrochloric acid in dioxane at 60°C overnight. Such methods are familiar to those skilled in the art.

The compounds of formula (II) can be prepared by reacting a compound of formula (III) or an acid addition salt thereof:



(III)

Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The carrier or diluent must be acceptable in the sense of being not deleterious to the recipient thereof. The pharmaceutically acceptable carrier or diluent may be, for example, binders (e.g., syrup, gum arabic, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone), excipients (e.g., lactose, sucrose, corn starch, potassium phosphate, sorbitol, glycine), lubricants (e.g., magnesium stearate, talc, polyethylene glycol, silica), disintegrators (e.g., potato starch), wetting agents (e.g., sodium laurylsulfate), and the like.

The routes for administration (delivery) of the composition of the invention include, but are not limited to, one or more of: oral (e. g. as a tablet, capsule, or as an ingestible solution), topical, mucosal (e. g. as a nasal spray or aerosol for inhalation), nasal, parenteral (e. g. by an injectable form), gastrointestinal, intraspinal, intraperitoneal, intramuscular, intravenous, intrauterine, intraocular, intradermal, intracranial, intratracheal, intravaginal, intracerebroventricular, intracerebral, subcutaneous, ophthalmic (including intravitreal or intracameral), transdermal, rectal, buccal, epidural, sublingual.

For example, the compound can be administered orally in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included. Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

A proposed dose of the compounds according to the present invention for administration to a human (of approximately 70kg body weight) is 0.1mg to 2g, more typically 0.1mg to 1g, of the active ingredient per unit dose, expressed as the weight of free acid. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition. The dosage will also depend on the route of administration. The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of the invention or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment or prevention will vary with the nature of the condition and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. Examples of other active agents that may be combined with the compound of formula (I) or a pharmaceutically acceptable derivative thereof include, but not limited to: (a) other VLA-4 antagonists; (b) H1 histamine antagonists; (c) NSAID's; (d) anti-diabetic agent e.g. glitazones (e) anti-cholinergic agents (f) COX-2 inhibitors e.g. 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (as disclosed in patent application WO 99/12930); (g) PDE-IV inhibitors; (h) steroids e.g. corticosteroids; (i) beta agonists; (j) antagonists of the chemokine receptors e.g. CCR-2, CCR-3, CCR-5 and CCR-8; (k) suitable multiple sclerosis treatments or preventions such as interferon; (l) LFA-1 antagonists; (m) TNF inhibitors; (n) Sulphasalazine and 5-aminosalicylates and (o) Immunosuppressants.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a

dihloromethane and a drop of dimethylformamide}. The reaction was stirred at 0°C for 1 hour and was then diluted with a saturated aqueous solution of sodium hydrogen carbonate (200 mL). After separation of the organic layer, the aqueous layer was re-extracted with dichloromethane (2 x 400 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated at reduced pressure. The product was purified by silica gel chromatography (Biotage 75L, 800 g silica) eluting with ethyl acetate: dichloromethane (3:97) to yield the title compound as a colourless solid; MS (ES+ve): $[M+H]^+$ at m/z 567, 569 ($C_{28}H_{27}BrN_2O_6$ requires $[M+H]^+$ at m/z 567, 569).

Preparation 12

(S)-2-{[1-(2-Bromo-5-methoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid ethyl ester (P12)

2-Bromo-5-methoxybenzoic acid (0.355 g, 1.54 mmol, Aldrich), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.168 g, 2 equiv.), and triethylamine (1.069 mL, 5 equiv.) were added to dimethylformamide (25 mL) under argon with stirring at room temperature. After 0.5 hour the ethyl ester corresponding to P7 (P13), (S)-2-amino-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid ethyl ester hydrochloride, (0.6 g, 1 equiv.) was added and stirring continued overnight. The solvent was then evaporated under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was washed with water (x 2) and saturated aqueous sodium bicarbonate before evaporation to dryness. The crude product was purified by column chromatography on silica with a gradient of 0-10% methanol in dichloromethane and subsequently by preparative HPLC to give the title compound.

MS (AP+ve): $[M+H]^+$ at m/z 567, 569 ($C_{28}H_{27}BrN_2O_6$ requires $[M+H]^+$ at m/z 567, 569).

Preparation 13

(S)-2-Amino-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid ethyl ester hydrochloride (P7 - corresponding ethyl ester) (P13)

Thionyl chloride (7.71 mL, 105.7 mmol) was added dropwise over 15 minutes to a solution of (S)-2-tert-butoxycarbonylamino-3-[4'-(hydroxyiminomethyl)-2',6'-dimethoxybiphenyl-4-yl]propionic acid ethyl ester (12.5 g, 26.5 mmol) [prepared analogously to the sequence P1-P6 except commencing in Preparation 1 with L-tyrosine ethyl ester hydrochloride (from Bachem) instead of L-tyrosine methyl ester hydrochloride] in dichloromethane (250 mL) at 0°C under argon. The reaction stirred for a further 15 minutes at batch temperature and then allowed to warm to room temperature and

was filtered, washed with water and dried at 40°C under vacuum to yield the title compound as an off-white solid.
^{1}H NMR δ (DMSO-d_6): 3.78 (6H, s), 7.0 (2H, s), 9.25 (2H, s)

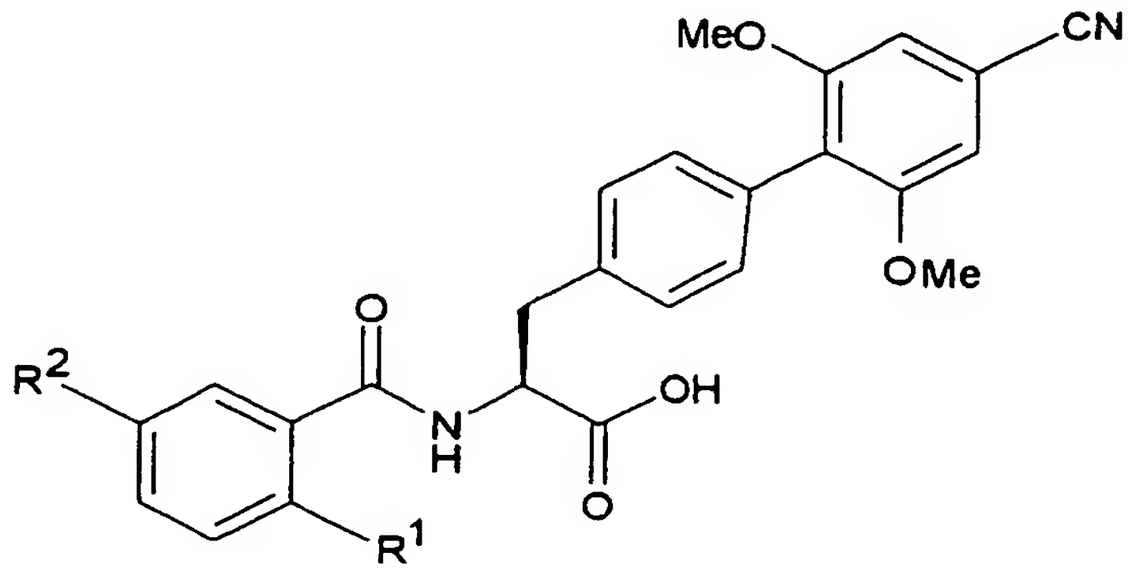
(S)-2-Amino-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid methyl ester hydrochloride

A solution of di-*tert*-butyldicarbonate (17.9 g, 81.8 mmol) in toluene (60 mL) was added dropwise to a solution of (S)-methyl tyrosine (from Flamma, 15.2 g, 77.9 mmol) in toluene (120 mL) at 90°C. The reaction mixture was stirred at 90°C for at least 30 minutes. Once complete by HPLC, the reaction mixture was cooled to 0°C and pyridine (19 mL, 0.23 mol) added keeping the temperature at 0°C. Trifluoromethanesulfonic anhydride (16.7 mL) was added dropwise keeping the temperature at 0°C. The orange slurry was stirred at 0°C for at least 2 hours. Once complete by HPLC 2M hydrochloric acid (133 mL) was added keeping the temperature at 0°C. The layers were separated and the upper organic layer washed with 10%w/w aqueous sodium carbonate solution (138 mL) and 36%w/w brine (138 mL). The organic layer was concentrated to approximately 60 mL and solid sodium chloride (30 g) added, followed by n-heptane (300 mL). The mixture was filtered and the filtrate extracted into 1-methyl-2-pyrrolidone (2x150 mL). Residual volatile organic solvents were distilled under vacuum. 4-Cyano-2,6-dimethoxyphenylboronic acid (17.5 g, 84.5 mmol) was added and the solution degassed. Tetrakis(triphenylphosphine) palladium(0) (3g, 2.7 mmol) and triethylamine (19.8 mL) were added and the reaction mixture heated to 70°C. The reaction was stirred at 70°C for at least 2 hours. Once complete by HPLC, the reaction mixture was transferred into another vessel and diluted with toluene (300 mL). 2M Hydrochloric acid (300 mL) was added and the mixture filtered. The organic layer was separated and washed with water (300 mL). The organic layer was filtered and washed through with toluene (90 mL). The toluene solution was stirred with Silicycle silica supported N-functionalised thiourea (11.7 g) for at least 15 hours. The silica was filtered and washed with toluene (30 mL). The solution was dried azeotropically then slowly added to a solution of hydrogen chloride in isopropanol (155 mL at 5M concentration) at 50°C. The reaction mixture was stirred at 50°C for 30 minutes until complete by HPLC. The mixture was cooled to 20°C and the product filtered off under vacuum and washed with toluene (60 mL). The solid was dried *in vacuo* at 40°C to yield the title compound as an off-white solid.

2-Bromo-5-hydroxybenzoic acid methyl ester

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable derivative thereof :



(I)

in which:

R^1 is bromo; and

R^2 is halogen, C_{1-6}alkyl or C_{1-6}alkoxy.

2. The compound according to claim 1 in which R^2 is halogen or C_{1-6}alkoxy.

3. The compound according to claim 2 in which R^2 is fluoro, methoxy or ethoxy.

4.(amended) The compound according to claim 1 which is selected from the group consisting of

(*S*)-2-{[1-(2-Bromo-5-methylphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid;

(*S*)-2-{[(2-Bromo-5-chlorophenyl)methanoyl]amino}-3-[4'-cyano-2',6'-dimethoxy)biphenyl-4-yl]propionic acid;

(*S*)-2-{[(2,5-Dibromophenyl)methanoyl]amino}-3-[4'-cyano-2',6'-dimethoxy)biphenyl-4-yl]propionic acid;

(*S*)-2-{[(5-(*iso*-Propoxy)-2-bromophenyl)methanoyl]amino}-3-[4'-cyano-2',6'-dimethoxy)biphenyl-4-yl]propionic acid

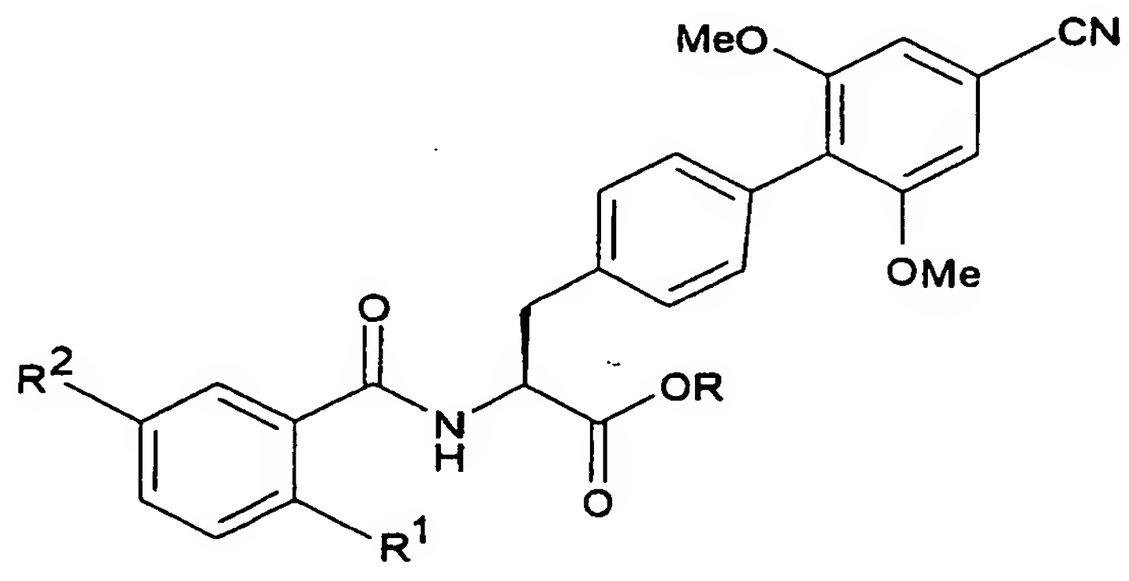
or a pharmaceutically acceptable derivative thereof.

5. (S)-2-{[1-(2-Bromo-5-ethoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid or a pharmaceutically acceptable derivative thereof.

6. (*S*)-2-{[1-(2-Bromo-5-fluorophenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid or a pharmaceutically acceptable derivative thereof.

7.(amended) (*S*)-2-{[1-(2-Bromo-5-methoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid or a pharmaceutically acceptable derivative thereof.

8. A process for the preparation of a compound of formula (I) which comprises hydrolyzing of a carboxylic acid ester derivative of formula (II):



(II)

in which R^1 and R^2 are as defined in formula (I) and R is a group capable of forming a carboxylic acid ester and optionally thereafter forming a pharmaceutically acceptable derivative thereof.

9. A compound according to any one of claims 1 to 7 for use in therapy.

10. A pharmaceutical composition which comprises a therapeutically effective amount of a compound according to any one of claims 1 to 7 in admixture with a pharmaceutically acceptable carrier or diluent.